EXHIBIT A164

Risk factors for familial and sporadic ovarian cancer among French Canadians: A case-control study

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OBJECTIVE: The objective was to compare risk factors between familial and sporadic ovarian cancer by means of a case-control approach.

STUDY DESIGN: We conducted a case-control study among French Canadian women in Montreal during 1995-1996. One hundred seventy women 20 to 84 years old with histologically confirmed diagnoses of primary ovarian carcinomas or borderline tumors were interviewed concerning their reproductive, family, and medical histories. During the same period 170 randomly selected population control subjects, frequency-matched to the case patients according to age and ethnic group, were also interviewed. Unconditional logistic regression methods were used for data analysis.

RESULTS: The major factors influencing the risk of development of ovarian cancer were as follows: (1) family history of breast or ovarian cancer, (2) a late age at use of oral contraceptives (a protective effect), and (3) a late age at last childbirth (a protective effect for familial case patients only).

CONCLUSION: These factors had equally great impacts in familial and sporadic cases, implying that the underlying mechanisms of carcinogenesis in sporadic and familial ovarian cancer may be similar and that hereditary ovarian cancer may be preventable. (Am J Obstet Gynecol 1998;179:403-10.)

Key words: Case-control, epidemiology, family history, ovarian cancer, risk factors

Ovarian carcinoma is difficult to detect in its early stages and is resistant to therapy in later stages. Of the 2000 patients with new cases of ovarian cancer diagnosed every year in Canada, approximately 1350 (67.5%) will die of the disease.[1] The age-standardized incidence of ovarian cancer in Canada for 1996 was estimated to be 12 cases/100,000 at-risk population. The strongest risk factor for ovarian cancer is a positive family history of ovarian or breast cancer. Among common adult tumors, ovarian cancer has among the highest proportions attributable to susceptibility genes.[2] Other risk factors include nulliparity, infertility, and a history of breast cancer.[3-8] Factors associated with a reduced risk include high parity, a history of tubal ligation or hysterectomy, and use of oral contraceptives.[8-10] Additional factors for which there is suggestive evidence include the use of talc, fertility drugs, and dietary factors.[11-13]

Mutations in both of the breast cancer genes, *BRCA1* and *BRCA2,* predispose women toward development of ovarian cancer.[14, 15] Ovarian cancer also appears as part of the spectrum of tumors seen in the hereditary nonpolyposis colorectal cancer syndromes.[16] From epidemiologic studies and mutation surveys, it appears that between 5% and 10% of ovarian cancers occur as a result of hereditary predisposition.[14, 15, 17-19] Familial ovarian cancer usually occurs in association with breast cancer (because of mutations in *BRCA1* and *BRCA2*), occasionally as ovarian cancer alone (*BRCA1*[20] or *BRCA2*), or with endometrial, colon, and other solid tumors (hereditary nonpolyposis colorectal cancer syndrome).[21] A family history of ovarian cancer is a strong risk factor for ovarian cancer, increasing with the number of first-degree relatives affected.[2] For families with 1 affected first-degree relative, the estimated lifetime risk increases 1.5 times to 3.6 times.[2-5, 18, 22-25] The population lifetime risk for ovarian cancer in North America is approximately 1:70. The risks rise with additional affected family members.

Families with ≥3 cases of ovarian cancer are generally

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Table I. Histologic characteristics of familial and sporadic ovarian tumors

	Familial (n = 58)	*Nonfamilial (n = 111)*	*Total (N = 169)**
Invasive	54 (93%)	93 (84%)	147
Serous	34	58	92
Endometrioid	7	16	23
Mucinous	5	10	15
Brenner	1	0	1
Clear cell	4	5	9
Mixed	3	4	7
Borderline (total)	4 (7%)	18 (16%)	22
Serous	3	11	14
Mucinous	1	7	8

*One woman did not have information on second-degree relatives, and it is therefore uncertain whether hers was a familial or sporadic case of ovarian cancer. The histologic examination of her tumor revealed a serous adenocarcinoma of the ovary.

considered to represent examples of hereditary ovarian cancer. Although many risk factors for ovarian cancer have been well documented, it is not yet known whether these risk factors apply equally well to the hereditary subgroup. Such knowledge would be important for women with a family history who were seeking information on how to reduce their risk. To address this issue we obtained detailed family histories and other risk factor information for 170 French Canadian women with ovarian cancer and 170 population-based French Canadian control subjects.

Material and methods

Case patients. After institutional review board approval was obtained, a total of 231 French Canadian women with a histologic diagnosis of ovary cancer were found through the gynecologic oncology clinics of 2 large Montreal teaching hospitals in 1995 and 1996. Of these, 48 (21%) were excluded from the study because they died before the interview (21 case patients), they refused to participate or were unavailable for follow-up (12 case patients), or they could not be contacted (15 case patients). A total of 183 case patients were interviewed, representing a response rate of 87% of the eligible living case patients. We later excluded 13 case patients because their ovarian tumors were not of epithelial origin, leading to a final total of 170 patients with ovarian carcinoma or with ovarian tumors of low malignant potential (borderline ovarian tumors). Of these case patients, 70% were interviewed directly in clinics and 30% were interviewed by phone. Each case patient had a histologically confirmed primary invasive carcinoma or a borderline tumor. Pathology records were systematically reviewed and tumors were classified as either serous, mucinous, endometrioid, clear cell, Brenner, or mixed tumors.

Control subjects. Population-based control subjects were obtained through a modified random-digit dialing method. To ensure that the age-distributions of case patients and control subjects were equal, a control subject was selected for each case patient from the page in the telephone directory where the case patient was listed. The names and addresses of 10 persons with the same first 3 digits of the telephone number as the patient were selected. These residences were then contacted by telephone. If there was no answer the number was called 7 more times during the day, the evening, and on weekends before being rejected. Respondents were questioned to determine whether the household contained a woman of self-reported French Canadian origin who matched the index case patient for age within 1 year and who agreed to be interviewed by telephone. If not, the procedure was repeated. A total of 750 households were contacted to obtain the control subjects. Five hundred (66.7%) did not reply or had no eligible women resident, and 10.7% refused to participate. A total of 170 subjects were interviewed.

Questionnaires. Questionnaires were administered in a standardized manner to all case patients and control subjects. The questionnaire was developed, evaluated, and tested within the Quebec Cancer Genetics Network in 1995 and was used at all study centers (Notre-Dame Hospital and Hôtel-Dieu Hospital, Montreal). The 57 questions concerned primarily reproductive factors (age at menarche, age at first childbirth, parity, age and cause of menopause) and medical history (use of hormone replacement therapy and oral contraceptives, tubal ligation, hysterectomy, other surgery), screening histories, and sociodemographic information (smoking, alcohol, education). A detailed family history of cancer was also taken in each case; this inquired about age of diagnosis and type of cancer in all female and male first-, second-, and third-degree relatives.

Statistical methods. In the case-control analysis of the data, relative risk estimates and corresponding 95% confidence intervals were calculated by unconditional logistic regression and maximum likelihood estimation. Multivariate unconditional logistic regression was used to allow for the simultaneous examination of multiple risk factors. Tests of statistical significance were based on differences in the log likelihoods, and all P values are 2-sided. Comparisons between continuously distributed variables were made with the Wilcoxon test. The Fisher exact test was used where appropriate. In the cohort analysis we used a univariate Cox proportional hazards model. The statistical analysis was conducted with the SAS software package (SAS Institute, Inc, Cary, NC).

Results

A total of 170 case patients with ovarian cancer and 170 population-based control subjects were interviewed in 1995. Case patients were born between 1910 and 1969, and their mean age at diagnosis was 53.7 years. Their

Table II. Cumulative incidences of cancer to the age of 70 years among first-degree relatives of case patients and control subjects

			Cox proportional hazards		
Site	*Case relatives (%)*	*Control relatives (%)*	*RR*	*95% CI*	*Significance*
Any					
Female	25.5	15.0	1.84	1.34-2.54	$P = .0002$
Male	19.4	11.8	1.65	1.10-2.49	$P = .015$
Both sexes	22.6	13.5	1.77	1.38-2.28	$P < .0001$
Breast	12.6	3.4	3.68	2.03-6.66	$P < .0001$
Ovary	2.7	2.3	1.32	0.52-3.34	$P = .56$
Prostate	1.4	0.9	1.67	0.28-10.0	$P = .57$
Colon					
Female	3.0	2.4	1.09	0.43-2.74	$P = .86$
Male	5.0	2.1	2.35	0.89-6.18	$P = .08$
Both sexes	4.0	2.3	1.59	0.82-3.06	$P = .17$
Leukemia					
Female	1.5	0.2	6.22	0.75-51.67	$P = .05$
Male	0.40	0.0	∞	—	$P = .15$
Both sexes	1.00	0.1	8.25	1.03-66.01	$P = .02$

RR, Relative risk; *CI,* confidence interval.

mean age at interview was 55.9 years, compared with a mean age of control subjects of 56.7 years. The distribution of the tumor types is presented in Table I.

Family history. We recorded current age, age at death, age at diagnosis of cancer, and cancer site in the relatives of case patients and control subjects. This enabled us to construct 2 historical cohorts, 1 composed of the relatives of case patients and the other of the relatives of control subjects. The cumulative incidence of cancer to the age of 70 years among the relatives of case patients compared with those of control subjects is shown in Table II. The risk of cancer was significantly higher among both female and male relatives of the case patients than those of the control subjects.

The relative risk of any cancer was 1.77 among the relatives of case patients with respect to the relatives of control subjects ($P < .0001$). It is surprising that the relative risks of any cancer were similar in the female and male relatives of the index case patients and control subjects (1.84 vs 1.65). There was a significant excess of breast cancer (relative risk 3.68, $P < .0001$) but not ovarian cancer (relative risk 1.32, $P = .56$) among the relatives of women with ovarian cancer. An eightfold excess of leukemia among the relatives of case patients was observed ($P = .017$).

Families with a total of ≥4 cases of ovarian cancer or of breast cancer in members <55 years old are generally considered to represent examples of hereditary cancer. Seven of the 170 case patients (4.1%) fit into this category. In the following analyses we refer to case patients with a positive family history as having familial cancer (≥1 person with breast cancer diagnosed at <55 years old or 1 other case of ovarian cancer in addition to the proband, on the same side of the family). Fifty-eight women satisfied this criterion. Some of these were due to predisposing genes and others were due to chance aggregations. The disease of case patients with a negative family history is referred to as sporadic.

The average age at onset of the familial case patients was younger than that of the sporadic case patients (51.2 vs 55.2 years; $P = .04$). The average age at onset of the invasive serous tumors was also younger for the familial cancers (54.0 years) than for the sporadic cancers (58.6 years). The distributions of the histologic subtypes were not different for the familial and sporadic invasive tumors (Table I). Only 7% of tumors in the familial group were borderline tumors, whereas 16% in the nonfamilial group were borderline tumors ($P = .09$). Surprisingly, there was no deficit of mucinous tumors among the familial ovarian cancer case patients (5/54 vs 10/93; Table I).

Reproductive, hormonal and other risk factors: Univariate analyses. Although case patients and control subjects did not significantly differ by age at menarche, familial case patients had menarche later (13.3 years) than did sporadic case patients (12.8 years, $P = .038$; Table III). The mean ages at first childbirth were similar for case patients and control subjects, but the mean age at last childbirth was significantly younger for case patients (29.0 years) than for control subjects (30.9 years, $P = .003$), suggesting that late childbirth is protective. Additionally, the mean age at last childbirth was younger for familial case patients (28.2 years) than for sporadic case patients (29.5 years, $P = .19$), suggesting that this protection may be stronger for familial case patients. The interval between first and last childbirth was significantly longer for the control subjects (mean 4.3 years) than for the case patients (mean 3.1 years, $P = .032$). Neither nulliparity nor low parity was a significant risk factor in this study.

As expected, the proportion of ovarian cancer case pa-

Table III. Reproductive factors and oral contraeptive use in control subjects, sporadic and familial ovarian cancer

	Case versus control					*Sporadic versus familial**				
	Control		*Case*			*Sporadic*		*Familial*		
	No.	*Mean*	*No.*	*Mean*	*P*	*No.*	*Mean*	*No.*	*Mean*	*P†*
Age at menarche (y)	170	12.7	169	13.0	.16	111	12.8	57	13.3	.038
Age at menopause‡ (y)	49	48.5	54	48.5	.99	39	48.5	15	48.3	.82
Parity	170	2.1	170	1.8	.16	111	1.8	58	1.8	.95
Age at first childbirth (y)	126	25.2	122	24.6	.28	79	24.8	42	24.3	.51
Age at last childbirth (y)	126	30.9	122	29.0	.0028	79	29.5	42	28.2	.19
Total No. of childbearing years	170	4.3	170	3.1	.032	111	3.3	58	2.8	.47
Use of oral contraceptives (% yes)	170	61.8	170	50.0	.038	111	46.8	58	55.2	.33
Oral contraceptive use duration (y)	152	4.0	154	2.5	.0065	102	2.7	51	2.2	.51
Age at first oral contraceptive use (y)	101	26.3	81	23.1	.0055	49	23.1	31	23.2	.96
Age at last oral contraceptive use (y)	87	32.9	69	28.6	.0016	43	29.5	25	27.6	.27
Tubal ligation (% yes)	170	21.2	169	13.6	.085	110	12.7	58	13.8	.82

Sporadic disease was defined as occurring in patients with no first-, second-, or third-degree relatives with breast cancer diagnosed at <55 years or with ovarian cancer at any age. *Familial* disease was defined as occurring in patients with ≥1 first-, second-, or third-degree relative with breast cancer diagnosed at <55 years or with ovarian cancer at any age.

*In 1 case the familial or sporadic status was unknown.

†The *P* value here compares the means of the sporadic with the familial case patients.

‡Age at menopause was limited to women <55 years old at diagnosis or survey and also to those women who had a natural menopause.

Table IV. Other factors

	Case versus control					*Sporadic versus familial*				
	Control		*Case*			*Sporadic*		*Familial*		
	No.	*% Yes*	*No.*	*% Yes*	*P*	*No.*	*% Yes*	*No.*	*% Yes*	*P**
Alcohol use	170	28.8	170	38.8	.066	111	39.6	58	36.2	.74
Perineal talc use	170	4.7	170	10.6	.064	111	9.91	58	12.1	.79
Breast surgery†	164	7.9	157	15.3	.053	107	19.6	49	6.12	.032
Abdominal surgery	170	38.8	169	36.6	.91	110	43.6	58	32.8	.19

*The *P* value here compares the means of the sporadic with the familial case patients.

†Included as having breast surgery were those who responded with: "nodule," "cyst," or "adenoma." Excluded were those who responded "breast cancers," "breasts implants," and "mammary reduction."

tients who had ever taken oral contraceptives was lower than for control subjects (50% vs 61.8%, $P = .038$). Familial case patients were as likely as sporadic case patients to have ever used oral contraceptives. The mean age at last use of oral contraceptives for all case patients was 28.6 years, compared with 32.9 years for control subjects ($P = .0016$), suggesting that late use of oral contraceptives is protective. Among oral contraceptive users, familial case patients had younger mean age (27.6 years) at last oral contraceptive use than did sporadic case patients (29.5 years), and they used oral contraceptives for a shorter total period (2.2 years) than did sporadic case patients (2.7 years). Although neither of these 2 comparisons were significantly different, they suggest that the protective effect of oral contraceptives may be stronger for familial case patients. In summary, compared with control subjects, case patients began taking oral contraceptives at a younger age but continued for a shorter period. This difference was more marked for the familial case patients. It should be noted that the differences between the subgroups in duration of use of oral contraceptives that we observed were rather small and nonsignificant and should therefore be interpreted cautiously. Significantly more case patients than control subjects had ever had previous breast surgery for nonmalignant conditions (Table IV), and perineal talc application was also more common in case patients. There were no significant differences between case patients and control subjects with respect to anthropometric variables.

Borderline tumors. Women with borderline tumors

Table V. Multivariate model

	All case patients (n = 153) versus control subjects (n = 152)			*Sporadic case patients (n = 101) versus control subjects (n = 152)*			*Familial case patients (n = 51) versus control subjects (n = 152)*		
	RR	*95% CI*	*P*	*RR*	*95% CI*	*P*	*RR*	*95% CI*	*P*
Age at diagnosis*	0.98	0.95-1.01	.14	0.99	0.96-1.02	.33	0.97	0.93-1.00	.06
Age at last childbirth†									
Never pregnant	0.63	0.33-1.19	.16	0.77	0.38-1.59	.48	0.46	0.18-1.21	.12
30-44 y	0.63	0.34-1.15	.13	0.80	0.41-1.58	.52	0.38	0.16-0.90	.027
Age at menarche‡	1.07	0.92-1.25	.40	1.01	0.85-1.20	.92	1.26	1.01-1.57	.041
Age at last oral contraceptive use§									
17-25 y	0.96	0.37-2.48	.93	0.84	0.28-2.55	.76	0.99	0.28-3.51	.99
25-35 y	0.26	0.12-0.57	.0007	0.25	0.10-0.62	.0027	0.26	0.08-0.79	.017
35-43 y	0.24	0.10-0.55	.0008	0.25	0.10-0.64	.0036	0.17	0.036-0.83	.028
Tubal ligation or hysterectomy‖	0.51	0.30-0.88	.016	0.51	0.27-0.95	.033	0.57	0.26-1.27	.17
Talc use¶	2.49	0.94-6.58	.066	2.45	0.85-7.07	.098	3.25	0.85-12.4	.084
Alcohol use									
0-4 drinks/wk#	1.58	0.75-3.33	.23	1.65	0.77-3.79	.23	1.28	0.46-3.61	.64
4-10 drinks/wk#	2.00	0.96-4.17	.063	2.58	1.17-5.68	.019	0.94	0.28-3.10	.92
≥10 drinks/wk#	0.46	0.13-1.69	.24	0.56	0.13-2.37	.43	0.30	0.033-2.71	.28

Ten case patients with no family history of breast or ovarian cancer (sporadic), 7 case patients with family history (familial), and 18 control subjects had missing observations for some of the covariates.
*Age at diagnosis for case patients or current age for control subjects, defined continuously.
†Age at last childbirth is defined categorically. Reference group is last childbirth at 17 to 29 years.
‡Age at first menstrual period, defined continuously.
§Age at last use of oral contraceptives, with baseline no use of oral contraceptives.
‖Tubal ligation or hysterectomy, yes versus no tubal ligation or hysterectomy (without oophorectomy), with baseline of no.
¶Use of talc on perineum, ever versus never, with baseline of never.
#Number of drinks per week, with baseline no drinks per week.

were younger (mean age at diagnosis of 44.4 years) than those with invasive tumors (mean age at diagnosis of 55.1 years). The risk for borderline tumors was less clearly reduced among women who had used oral contraceptives. The mean duration of oral contraceptive intake among women with borderline tumors (4.05 years) was greater than among those with invasive carcinoma (2.31 years). As with invasive cancers, nulliparity was not a risk factor for borderline tumors (relative risk 0.75, $P = .61$).

Multivariate analysis. We incorporated all the significant variables from the univariate analysis into the final unconditional logistic regression model. In the model we also included other variables that had previously been reported to be of possible etiologic relevance but were of borderline significance in the univariate analysis in our study (Table V). The most striking finding in the adjusted analysis is that for all categories of case patients versus control subjects a late age at last use of oral contraceptives is a strong protective factor (relative risk 0.24, $P = .0008$). Various models were assessed, and age at last oral contraceptive use resulted in lower P values and –2 log likelihood values than did age at first use or duration of oral contraceptive use (Table III and data not shown). We therefore used the former parameter in the multivariate analysis. Tubal ligation or hysterectomy (without oophorectomy) was a protective factor (relative risk 0.51, $P = .016$). Use at any time of talc in the perineal region was a positive risk factor (relative risk 2.49), but this result did not reach significance. Moderate alcohol consumption was a positive risk factor for ovarian cancer (relative risk 2.00), but this result was not statistically significant ($P = .063$).

For case patients with a stronger family history of breast or ovarian cancer (≥1 other family members with breast cancer at age <55 years or ovarian cancer at any age), the effects of age at menarche, age at last oral contraceptive use, tubal ligation, and perineal talc application appear to be as strong as, or stronger than, those in the sporadic case patients (Table V). Of particular note is that a late age at last childbirth is highly protective against ovarian cancer in women who have ≥1 other relative with ovarian cancer or breast cancer diagnosed at age <55 years (relative risk 0.38, $P = .027$).

Comment

Family history. We estimate that the hereditary proportion of ovarian cancer in the French Canadian population of Quebec is between 4% and 10%. The lower estimate is based on the observation of 7 families with ≥4 relatives with breast cancer diagnosed at <55 years (or ovarian cancer at any age) among 170 unselected case patients. The higher estimate includes the 17 families with ≥3 such patients (including the index case patient herself). Narod et al[19] used slightly more stringent criteria to estimate that the hereditary fraction of ovarian cancer in southern Ontario was approximately 3% to 7%. They noted that the estimated hereditary proportions of ovarian cancer may be different in other populations,

Table VI. Effect of duration of use of oral contraceptives on risk of ovarian carcinoma

	Duration of oral contraceptive use				
	0-1 y	*1-5 y*	*6-10 y*	*11-25 y*	*Total*
Control subjects	66	35	35	16	152
Case patients	88	36	23	7	154
TOTAL	154	71	58	23	306
Relative risk	1.0	0.77	0.49	0.33	—
95% confidence interval	—	0.44-1.36	0.27-0.91	0.13-0.82	—
P	—	.39	.03	.024	—

both because the frequencies of susceptibility mutations may differ and because varying fertility patterns may lead to differences in average family size. Thus the slightly higher figure reported here, for a province with a relatively small founding population, an established increased incidence of some genetic diseases,[26] and typically large family sizes, is consistent with figures from the Ontario study.

Analyzing the data as a case-control study (rather than as a cohort study), we observed a relative risk of 1.93 (95% confidence interval 0.85 to 4.38) for a family history of ovarian cancer in any first-, second-, or third-degree relative. This figure is comparable to that reported in previous case-control studies. It is apparent that a family history of ovarian cancer is probably the strongest risk factor for ovarian cancer. One strength of our study is that we have included information on breast cancer in the relatives. This is important because breast cancer is more common than ovarian cancer and because breast cancer is more likely to occur in a *BRCA1*- or *BRCA2*-positive pedigree than is ovarian cancer. Thus if we are attempting to determine the hereditary contribution to ovarian cancer, we must question ovarian cancer case patients about both ovarian and breast cancer in their families.

Two genes (*BRCA1* and *BRCA2*) that predispose toward development of ovarian cancer have been identified, and it is possible to directly determine the proportion of ovarian cancer attributable to mutations in these genes. A number of studies have estimated that this proportion is 3% to 26%, depending on the population and the gene studied.[14, 15, 27-31] The absence of a family history does not rule out the possibility of a mutation in *BRCA1* and *BRCA2,* even in cases in which the mutation is known to be of ancient origin. In this study we did not analyze the case patients for mutations, but it will be interesting to determine the frequencies of *BRCA1* and *BRCA2* mutations among French Canadian women with ovarian cancer.

We used a historical cohort approach to analyze the data; this increases the information that can be gathered from the pedigree. In this study there was an overall excess of cancer at all sites in men and women, with leukemia (relative risk 8.25, 6 cases observed, 1 case expected) showing the largest relative risk (Cox proportional hazard relative risk, Table II). Among female first-degree relatives of case patients, breast cancer was seen in significant excess compared with relatives of control subjects (relative risk 3.68, $P = .0001$). Interestingly, there was no significant excess of ovarian cancer (relative risk 1.32, $P = .56$). Among male relatives the relative risk for colon cancer was 2.35 (13 cases observed, 6 expected, $P = .075$). There was no excess of colon cancer among female relatives. Previous case-control studies of ovarian cancer have shown that ovarian,[2-5, 18, 22-25] breast,[5, 25] colon,[4] pancreatic,[2] and prostate cancers[4] are all significantly overrepresented among the relatives of women with ovarian cancer. However, only the Utah study[2] was able to study distant relatives systematically, and only our study used a historic cohort approach to calculate the relative risks in a proportional hazards model. In a study of the first-degree relatives of women with breast, ovarian, or endometrial cancer, a significant excess of ovarian and breast cancer was seen among the relatives of women with either breast or ovarian cancer.[32] In fact, the risk of breast cancer was not significantly different for women with a family history of ovarian cancer rather than breast cancer. A record linkage study from Iceland[33] also showed a significant 90% excess of ovarian cancer among the first-degree relatives of women with breast cancer. However, this was not seen in the United Kingdom Office of Population, Censuses and Surveys studies of ovarian and breast cancer.[34, 35] Thus, considering all studies together, it is likely that a personal history of ovarian cancer is significantly associated with a family history of breast or ovarian cancer, and a family history of breast cancer should always be sought in any woman at risk for ovarian cancer.

Oral contraception, reproductive risk factors, and tubal ligation. The most striking findings in our study are the protective effects of late use of oral contraceptives, a long interval between first and last live childbirth, and a late age at last childbirth (Tables III and V). Many other studies have shown oral contraceptive use to be inversely associated with ovarian cancer. Hankinson et al[10] reana-

lyzed 20 epidemiologic studies and found a summary relative risk of 0.64 (95% confidence interval 0.57 to 0.73) for use of oral contraceptives at any time. They also found that the effect was strongest in women who had >5 years of use. By contrast, in a reanalysis of 12 US case-control studies no extra protective effect after 6 years of use was found.[8] In our study we found that an increasing duration of use of oral contraceptives was associated with a decreasing risk (relative risk 0.89, $P = .00013$) for each year of use and, unlike Whittemore et al,[8] we observed no diminution of effect with increasing number of years of use. In fact we noted a marked trend toward increasing protection against ovarian carcinoma with increasing duration of use of oral contraceptives (Table VI). Among women who had used oral contraceptives for >6 years, there was a suggestion that oral contraceptive use was more protective for those who continued use beyond 10 years rather than stopping after 10 years (the relative risk for 11 to 25 years of use vs 6 to 10 years of use was 0.67, $P = .61$). Compared with those who took oral contraceptives for <5 years, those with 11 to 25 years of use resulted in a relative risk of 0.43 ($P = .10$). Hormone replacement therapy has not been shown to be a risk factor for ovarian cancer,[8] and this finding was confirmed in our study.

An early age at menarche is a risk factor for ovarian cancer, but the risk increase is relatively small, ranging from 1.2 to 1.5 when comparing commencement of menarche at <12 years with commencement at >15 years.[36] In our study case patients and control subjects did not significantly differ with respect to age of menarche, but familial case patients had menarche later (13.3 years) than did sporadic case patients (12.8 years, $P = .038$; Table III). This difference was maintained in the multivariate analysis (Table V). High parity is protective,[8] but in this study we showed that in an adjusted analysis a late age at last childbirth and a long interval between first and last live childbirth were more important than the total number of pregnancies or the age at first childbirth (Table V). A large, nested case-control study from Sweden showed that a late age at first childbirth was more protective than high parity.[7] In the review by Parazzini et al[36] of 16 previous studies, however, only 1 suggested that a late first childbirth was more protective than an early first childbirth. It is intriguing that in a study of *BRCA1* carriers a late age at last childbirth was protective against ovarian cancer and there was no increased risk associated with nulliparity.[37] There also was no protective effect of high parity against familial ovarian cancer in the Utah study.[2]

We found that tubal ligation or hysterectomy (without oophorectomy) was protective (adjusted relative risk 0.51, $P = .016$; Table V). There was no change in the point estimates of the risk reduction among those with a family history of breast or ovarian cancer compared with those without a family history. Tubal ligation has previously been associated with a reduced risk of ovarian cancer. In a large, prospective study, Hankinson et al[9] observed a strong inverse association between tubal ligation and ovarian cancer that persisted after adjustment for age, oral contraceptive use, parity, and other ovarian cancer risk factors (relative risk 0.33, 95% confidence interval 0.16 to 0.64). They also noted a weaker inverse association between simple hysterectomy and ovarian cancer. The protective effect of hysterectomy is increased if the operation is carried out at a younger age.[8, 9] Whether tubal ligation has its effect by preventing external carcinogenic agents from reaching the ovary or by alteration of the local environment of the ovary is not known.

Alcohol and talc as potential risk factors for ovarian cancer. In this study we found that moderate alcohol consumption (between 4 and 10 drinks per week compared with no alcohol use) was nonsignificantly associated with ovarian cancer (relative risk 2.00, $P = .063$). Other studies have also reported that moderate to high alcohol consumption is nonsignificantly associated with ovarian cancer.[12, 13, 38] Perineal talc use was a nonsignificant risk factor in our study (relative risk 2.49, $P = .064$). Talc has been previously implicated in the development of ovarian cancer.[11, 13] Although there are reports of talc embedded in human ovarian tissue and of talc migrating through the human female reproductive tract, the literature reviewed does not provide any convincing evidence that pure cosmetic talc, when used as intended, presents a health risk to women.[11, 39, 40]

Familial and sporadic ovarian cancer: Are the risk factors the same? Early detection of ovarian cancer is difficult. No screening procedure has been shown to reduce mortality rates, and no single test has yet proved to be practical for population screening. However, it is possible that those at higher risk may be more likely to benefit from screening procedures, because the positive predictive value of a screening test depends in part on the prevalence of the disease in the population under study. The inherited fraction of ovarian cancer in this study is between 4% and 10%, and perhaps we should direct our preventive and early detection efforts toward these women at higher risk. Women with a family history of ovarian cancer are more likely to carry mutations in highly penetrant cancer-predisposing genes. The findings of this study raise the possibility that preventive measures such as oral contraceptive use and tubal ligation may be effective in preventing ovarian cancer in persons at high risk. The findings that a late age of last use of oral contraceptive, a late age of last childbirth and a prolonged interval between first and last childbirth are protective suggest that the timing of the intervention is important. For example, hysterectomy appears to be most protective when it is carried out in the early to middle

40s.[8, 9] Anovulation appears to be a protective state for ovarian cancer, but the protective effects of oral contraceptive and pregnancy may change with time.[41]

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